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Elizabeth Barksdale Boyle
Westat

Nicole C. Deziel
Yale University

Bonny L. Specker
South Dakota State University, Bonny.Specker@sdstate.edu

Scott Collingwood
University of Utah

Clifford P. Weisel
Rutgers University - New Brunswick/Piscataway

See next page for additional authors

Authors
Elizabeth Barksdale Boyle, Nicole C. Deziel, Bonny L. Specker, Scott Collingwood, Clifford P. Weisel, David J. Wright, and Michael Dellarco

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Elizabeth Barksdale Boyle [a,*], Nicole C. Deziel [b], Bonny L. Specker [c], Scott Collingwood [d], Clifford P. Weisel [e], David J. Wright [a], Michael Dellarco [f]

[a] Westat, 1600 Research Blvd, Rockville, MD, United States
[b] Yale University School of Public Health, Department of Environmental Health Sciences, New Haven, CT, United States
[c] South Dakota State University, Ethel Austin Martin Program in Human Nutrition, Brookings, SD, United States
[d] University of Utah, Department of Pediatrics, Salt Lake City, United States
[e] Rutgers University, Environmental & Occupational Health Science Institute (EOHSI), Piscataway, NJ, United States
[f] Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, United States

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ABSTRACT

Background: Birth cohort studies provide the opportunity to advance understanding of the impact of environmental factors on childhood health and development through prospective collection of environmental samples.

Methods: We evaluated the feasibility and informative value of the environmental sample collection methodology in the initial pilot phase of the National Children's Study, a planned U.S. environmental birth cohort study. Environmental samples were collected from January 2009–September 2010 at up to three home visits: pre-pregnancy ($n=306$), pregnancy ($n=807$), and 6-months postnatal ($n=117$). Collections included air for particulate matter ≤ 2.5 μm ($PM_{2.5}$), nitrogen dioxide, ozone, volatile organic compounds (VOCs), and carbonyls; vacuum dust for allergens/endotoxin; water for VOCs, trihalomethanes (THMs), and haloacetic acids (HAAs); and wipe samples for pesticides, semi-volatile organics, and metals. We characterized feasibility using sample collection rates and times and informative value using analyte detection frequencies (DF).

Results: Among the 1230 home visits, environmental sample collection rates were high across all sample types (mean=89%); all samples except the air $PM_{2.5}$ samples had collection times <30 min. Informative value was low for water VOCs (median DF=0%) and pesticide floor wipes (median DF=5%). Informative value was moderate for air samples (median DF=35%) and high for water THMs and HAAs (median DF=91% and 75%, respectively).

Conclusions: Though collection of environmental samples was feasible, some samples (e.g., wipe pesticides and water VOCs) yielded limited information. These results can be used in conjunction with other study design considerations, such as target population size and hypotheses of interest, to inform the method selection of future environmental health birth cohort studies.

1. Introduction

Increasing recognition that exposure to environmental chemicals during fetal development or early childhood may be linked to adverse pregnancy outcomes, childhood and adult morbidity, and mortality has prompted the implementation of numerous birth cohort studies worldwide (Wigle, 2003; Branum et al., 2003). In the United States, five birth cohort studies funded by the Environmental Protection Agency (EPA) and National Institute of Environmental Health Sciences (NIEHS), were launched from 1998–2003, each focusing on the relationship between exposures to select classes of environmental chemicals, such as pesticides, metals, or endocrine disrupters, and infant growth and development within populations in focused geographic areas (e.g, New York City, Salinas Valley, CA) (Kimmel et al., 2005; Eskenazi et al., 2005). More than 37 European birth cohort studies are

Abbreviations: 4,4′-DDD, Dichlorodiphenyldichloroethane; 4,4′-DDE, Dichlorodiphenyldichloroethylene; 4,4′DDT, Dichlorodiphenyltrichloroethane; HAAs, Haloacetic acids; IQR, interquartile range: 25th-75th percentiles; LOD, Limit of Detection; MTBE, Methyl tert-butyl ether; NCS, National Children's Study; NO_2, Nitrogen dioxide; O_3, Ozone; $PM_{2.5}$, Particulate matter 2.5 μm diameter; RR, Relative Risk; THMs, Trihalomethanes; VOCs, Volatile organic compounds

* Correspondence to: Board on Environmental Studies and Toxicology, National Research Council of The National Academy of Sciences, 500 Fifth Street NW (618), Washington D.C. 20001, United States.
E-mail address: eboyle@nas.edu (E. Barksdale Boyle).

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investigating the effects of a wide array of environmental exposures during pregnancy or early childhood and child health (Gehring et al., 2013; Vrijheid et al., 2012). Likewise, large-scale studies of the effects of environmental chemical exposures on maternal and child health have been conducted in Canada, Japan, and Korea (Ha et al., 2011; Kawamoto et al., 2014; Arbuckle et al., 2013). These studies have used a combination of indirect methods, such as questionnaires and modeling, as well as direct methods, such as biomarkers and environmental sample collection, to characterize environmental exposures (Gehring et al., 2013; Vrijheid et al., 2012).

The US National Children's Study (NCS) is a birth cohort study that planned to enroll and follow 100,000 children throughout the United States from before birth through age 21 years (Baker et al., 2014). Broad in scope and with a large sample size, detailed environmental exposure assessment methods were proposed, including questionnaires, observations, biological specimens, and environmental samples (Landrigan et al., 2006). Measurement of chemicals in environmental samples was one of the key exposure assessment approaches considered for the NCS, because it is objective, non-invasive, and potentially provides information about sources and routes of exposure. Environmental samples can be particularly useful when biomarkers are not available or have very short half-lives or when questionnaires are impractical or not validated (Needham et al., 2005; Ozkaynak et al., 2005). However, environmental sample collection can be costly compared to less direct exposure measures (Whitmore et al., 2005). In 2009, the NCS began its pilot study ("the Vanguard Study") to evaluate data collection methodologies and protocols. Following the 2014 National Academies of Sciences assessment of the NCS, (Institute of Medicine and National Research Council, 2014) the National Institutes of Health Advisory Committee to the Director recommended discontinuation of the NCS (NIH, 2014). Notwithstanding these events, the results from the NCS Vanguard Study are valuable and can provide critical information to epidemiologists planning future children's environmental health studies. The current paper reports on the ability to collect samples (feasibility) and the utility of the information obtained to observe an exposure-disease relationship (informative value) from the environmental samples collected at home visits during the initial phase of the NCS Vanguard Study from 2009–2010.

2. Materials and methods

2.1. Study population

As described previously (Baker et al., 2014), 1399 women were enrolled in the NCS initial Vanguard Study from 2009–2010 from seven locations: Queens County, New York; Duplin County, North Carolina; Salt Lake County, Utah; Orange County, California; Montgomery County, Pennsylvania; Waukesha County, Wisconsin; and four adjacent counties in South Dakota (Brookings County) and Minnesota (Yellow Medicine County, Pipestone County and Lincoln County) (Baker et al., 2014). The initial Vanguard Study protocol included up to three home visits per participant: pre-pregnancy (women likely to become pregnant, $n=306$), pregnancy (any trimester, $n=807$), and child 6-month (6 months after birth, $n=117$). All home visits included environmental sample collection, an interview, biospecimen collection, a physical exam, and an observational walk-through of the residence. Participants could refuse any portion of a study visit.

2.2. Environmental sample collection

The NCS Research Plan of 2007 defined study hypotheses about specific environmental exposures and health outcomes (NCS, 2007). Several hypotheses related prenatal exposures to health outcomes in children; these hypotheses determined the chemicals measured in the environmental samples. One hypothesis suggested exposure to air pollutants (e.g., carbonyls, O_3, NO_2, $PM_{2.5}$, and VOCs) may increase risk of asthma development (McConnell et al., 2002; Brauer et al., 2002; Delfino et al., 2003; Corradi et al., 2003). Another suggested to exposure to disinfection byproducts in tap water (e.g, THMs and HAAs) may have a negative impact on fetal growth and development (Hinckley et al., 2005). A third suggested exposure to allergens and endotoxin may increase risk of developing asthma and allergies (Lau et al., 2005). A fourth suggested exposure to persistent chemicals (e.g., metals, pesticides, and SVOCs, and polychlorinated biphenyls) may increase risk of neurodevelopmental problems in children, such as decreased intelligence and increased risk of attention deficit hyperactivity disorder (Palmer et al., 2006; Eskenazi et al., 1999; Daniels et al., 2003).

Environmental sampling methods for the NCS were selected based on review of the literature and review of protocols from other studies, such as the National Human Exposure Assessment Survey (NHEXAS), National Health and Nutrition Examination Survey (NHANES), and American Healthy Homes Survey (AHHS). The criteria for selection of sampling methodology in the NCS included validity of method, collection efficiency, successful implementation in prior environmental health studies, cost, and logistical feasibility. The environmental sample collection protocols for each visit are described in Table 1. To reduce costs and participant burden, some samples were only collected from a random subset of participants or when a specific source was identified in the home. The pre-pregnancy visit protocol included one air sample (fine particulate matter [$PM_{2.5}$]) and one wipe sample (pesticides). Two air samples (carbonyls and volatile organic compounds [VOCs]) were randomly collected in 10% of homes.

The pregnancy visit protocol included one vacuum sample of fine dust for analysis of allergens and endotoxin and three wipe samples for analysis of pesticides, metals, semi-volatile organic compounds (SVOCs). A water sample was scheduled for all homes served by a private well or unknown water source for analysis of VOCs. Water samples for analysis of disinfection byproduct samples (trihalomethanes [THMs] and haloacetic acids [HAAs]) were collected from 10% of homes served by a municipal water supply. The child 6-month visit protocol included two air samples for analysis of $PM_{2.5}$ and carbonyls, one vacuum sample for analysis of allergens and endotoxin, and three wipe samples for analysis of pesticides, metals, and SVOCs. Air VOCs samples were scheduled for collection in 10% of homes. Collection of air nitrogen dioxide (NO_2) and air ozone (O_3) samples were planned for 100% of homes with an indoor source, such as a gas stove (NO_2) and a laser-jet printer (O_3). Additionally, NO_2 and O_3 samples were scheduled for collection in 3% and 5% of homes with no identified source, respectively. At all visit types, procedures specified that collection status (collected/not collected), reason for non-collection, and collection location information were to be recorded on hard-copy sample collection forms.

2.3. Air sampling and analysis

$PM_{2.5}$ was collected with active air sampling, while carbonyls, VOCs, NO_2, and O_3, were collected passively. The samples were placed in the room most often used by the participant (mother or child depending on the visit), other than the kitchen, for 6–8 days. The kitchen was excluded because it is generally not the most-used room and concern that inconvenient placement could lead to non-compliance. $PM_{2.5}$ samples were collected using a personal environmental monitor (SKC, Eighty-Four, PA) with a

Table 1
Collection rates of environmental samples, by sample and visit type, and environmental sample collection schedule in the NCS Vanguard Study (2009–2010).

Visit type	Sample type	Hypothesized outcome	% visits targeted	No. collected	No. scheduled	% collected
Pre-pregnancy	Air carbonyls	Asthma	10	30	33	91
	Air $PM_{2.5}$	Asthma	100	251	306	82
	Air VOCs	Asthma	10	30	33	91
	Wipe pesticide	Neurodevelopmental outcomes	100	275	306	90
Pregnancy	Vacuum Allergens/ endotoxin	Allergies	100	722	807	89
	Water HAA	Adverse birth outcomes	10% of homes without a private well	71	71	100
	Water THMs	Adverse birth outcomes	10% of homes without a private well	71	71	100
	Water VOCs	Adverse birth outcomes	100% of homes served by a private well or with unknown water source	75	79	95
	Wipe metals	Neurodevelopmental outcomes	100	751	807	93
	Wipe pesticide	Neurodevelopmental outcomes	100	741	807	92
	Wipe SVOC	Neurodevelopmental outcomes	100	738	807	91
Child 6-month	Air carbonyls	Asthma	100	87	117	74
	Air NO_2	Asthma	2–3% without a flame source, 100% with source	62	70	89
	Air O_3	Asthma	5% without a laser printer or air cleaner, 100% with source	17	18	94
	Air $PM_{2.5}$	Asthma	100	78	117	67
	Air VOCs	Asthma	10	–[a]	–[a]	89
	Vacuum Allergens/ endotoxin	Allergies	100	95	117	81
	Wipe metals	Neurodevelopmental outcomes	100	101	117	86
	Wipe pesticide	Neurodevelopmental outcomes	100	98	117	84
	Wipe SVOC	Neurodevelopmental outcomes	100	98	117	84

Abbreviations: HAAs, haloacetic acids; $PM_{2.5}$, particulate matter 2.5 μm diameter; NO_2, nitrogen dioxide; O_3, ozone; SVOCs, semi-volatile organic compounds; THMs, trihalomethanes; VOCs, volatile organic compounds.

[a] Value not displayed as it is below the NCS disclosure threshold.

37 mm, 0.8 μm, PTFE filter connected to a Leland Legacy pump calibrated to 2 L/min (SKC, Eighty-Four, PA). The pump was programmed to cycle for 8 min on/14 min off until a total run time of 3672 min was reached (i.e, for 7 days). The $PM_{2.5}$ filters were gravimetrically analyzed by EMSL Analytical (Cinnaminson, NJ) using U.S. EPA IP-10A (EPA, 1989). Carbonyls samples were collected using the Assay Tech AT X571 sampler (Livermore, CA) and analyzed for 9 carbonyls by EMSL Analytical (Cinnaminson, NJ) using U.S. EPA TO-11A (U.S. EPA, 1999). The air VOCs sample was collected with a 3M 3500 Organic Vapor Monitor (St. Paul, MN) and analyzed by EMSL Analytical (Cinnaminson, NJ) for 14 compounds using GC–MS following standard methods (EPA, 2005; CDC, 2000) NO_2 and O_3 samples were collected with Ogawa samplers (Pompano Beach, FL) with a cellulose filter treated with either triethanolamine (NO_2 samples) or nitrite (O_3 samples) and analyzed by RTI International (Research Triangle Park, NC) using Ogawa ion chromatography methods (Ogawa and Company, 2001, 2006).

2.4. Vacuum dust sampling and storage

The vacuum allergens/endotoxin sample was a composite sample collected from the participant's bedroom from a one square yard (1-yd^2) area from the bed and floor using a DUSTREAM™ dust collector (Indoor Biotechnologies, Charlottesville, VA) and Mighty Mite vacuum cleaner (Eureka, Charlotte, NC) following the National Health and Nutrition Examination Survey (NHANES) Allergen Dust Collection Procedure (CDC, 2014a). The vacuum allergen/endotoxin samples were shipped to the NCS Repository (Fisher Bioservices, Rockville, MD) and stored for future analysis.

2.5. Wipe sampling and analysis/storage

The wipe samples were collected using Ghost Wipes (Environmental Express, Charleston, South Carolina), pre-packaged polyvinyl alcohol wipes wetted with water. The pesticide and SVOC wipe samples were collected from a one square foot (1-ft^2) area on a hard surface floor of the participant's most used room or the kitchen if the most used room was carpeted. The metals wipes were collected from a one square foot area in the most used room regardless of flooring type, carpet or smooth flooring. The pesticide wipes were analyzed for 28 chemicals at Southwest Research Institute (San Antonio, TX) using the American Healthy Homes Study protocol (Stout et al., 2009). The SVOCs and metals wipes were stored for future analysis.

2.6. Water sampling and analysis

All water samples were collected from a household tap following standard EPA Methods (Domino et al., 2003; EPA, 1995) and analyzed by Underwriters Laboratories, Inc. (South Bend, IN) using EPA Method 552.3, Rev 1.0 for HAA analyzes (Domino et al., 2003) and EPA Method 524.2, Rev 4.1 for THM and VOC analyzes (EPA, 1995). Water samples were analyzed for 9 HAAs, 4 THMs, and 85 VOCs, of which only 13 were detected.

2.7. Statistical methods

We characterized feasibility (i.e., the ability to collect the samples) by calculating sample collection rates and times. Sample collection times were calculated as the difference between start and stop times as recorded by field staff on sample collection forms. Because barriers to sample collection could vary by geographic region due to issues such as transportation or cultural concerns, we examined whether sample collection rates and times differed by urban (Queens, Orange County, Salt Lake City, and Montgomery PA) and rural (South Dakota and Minnesota, Duplin NC, and Waukesha WI) study location. We also evaluated the reasons samples were not collected, such as participant refusal, supply problems, equipment problems, or the field staff ran out of time. Numbers < 10 are not presented in the tables below due to NCS rules disclosure guidelines.

We characterized informative value, or the utility of the

information obtained from the environmental samples to evaluate an exposure–disease relationship, with analyte detection frequencies and by the sample size required to obtain a given apparent relative risk (apparent relative risk, not true relative risk, as we have not accounted for plausible misclassification in neither disease nor exposure). We calculated a sample size estimate, (Snedecor and Cochran, 1980) assuming a binary categorization of exposure, 80% power, a two-sided alpha = 0.05 for three disease prevalences: 0.2% (e.g., musculoskeletal birth defects), (Parker et al., 2010) 1.5% (e.g., autism), (CDC, 2014b) and 10% (e.g., asthma) (Bloom et al., 2013). Categorized exposure as follows, for samples with a median detection frequency > 50%, we used an exposure prevalence of 50%, assuming one could dichotomize the exposure based on the median concentration, otherwise we used the median detection frequencies found for each sample type (35%, 20%, and 5%). We calculated sample sizes for 1.4, 2.5, and 5.0 obtained from the 25th, 75th, and 90th percentiles reported in a review of epidemiologic literature (Kavvoura and Liberopoulos, 2007). The informative values of the vacuum dust, metal wipes, and SVOC wipes are not discussed because they were placed in storage for future analysis.

3. Results

3.1. Feasibility

Sample collection rates ranged from 67% (air $PM_{2.5}$ at child 6-month visit) to 100% (water THMs and HAAs at pregnancy) across all samples and visit types with a mean of 89% (Table 1). The sample collection rates at the child 6-month visit tended to be lower than at the other two visits with mean sample collection rates across all samples types of 86%, 92%, and 81% for the pre-pregnancy, pregnancy, and child 6-month visits, respectively. Looking at overall sample collection rates, the water samples had the highest sample collection rate (98%), followed by the wipe (91%), vacuum (88%), and air samples (80%). We stratified these overall sample collection rates by urban/rural location, but these differences were not significant (not shown). We were unable to evaluate reasons for non-collection, because the sample collection form was not completed for > 80% of uncollected samples.

Table 2 presents the field environmental sample collection times by sample type and visit. Nine environmental sample types had a median collection time < 30 min, less than half the time it takes to complete the participant interview. The least time-consuming samples were the wipe samples at the pre-pregnancy visit (median collection time = 8 min) and water VOCs samples at the pregnancy visit (median collection time = 10 min). The vacuum allergens/endotoxin samples at the pregnancy and child 6-month visits were moderately time-consuming with a median collection time of 20 min at each visit. The most time-consuming collection was the child 6-month visit air samples (median collection time = 46 min) which included up to 5 separate samples; followed by the pre-pregnancy visit air samples (median collection time = 39 min which included a maximum of 3 separate samples. Only the water sample collection times differed by rural vs. urban (not shown). Median water sample collection time for urban homes, generally requiring two collections (THMs and HAAs), was 6 min longer than the median collection time for rural homes, which generally only required one collection (VOCs).

3.2. Informative value

The informative values of the different sample types (air, water, wipe) are presented in Tables 3–6. Of the 26 air sample analytes, 10 were detected at a rate > 50%: $PM_{2.5}$, NO_2, the carbonyls benzaldehyde, formaldehyde, and hexanaldehyde, and the VOCs benzene, *d*-limonene, *α*-pinene, toluene, and *m,p*-xylenes (Table 4). Samples with this detection frequency required estimated sample sizes from 35 (disease prevalence 10%, relative risk 5) to 93,000 (disease prevalence 0.2%, relative risk 1.4) (Table 6). The air O_3, air VOCs, and air carbonyls had median detection frequencies of 36%, 38%, 22% respectively (Table 4). With the detection frequency of approximately 35%, required sample sizes ranged from 40 (disease prevalence 10%, relative risk 5) to 104,000 (disease prevalence 0.2%, relative risk 1.4). With detection frequency of approximately 20%, the air carbonyls samples would require sample sizes range from 50 (disease prevalence 10%, relative risk 5) to 150,000 (disease prevalence 0.2%, relative risk 1.4) (Table 6).

Of the 28 pesticide wipe analytes, none were detected at a frequency > 50% (Table 4). The pyrethroids; *cis*-permethrin (48%), *trans*-permethrin (48%), bifenthrin (32%), and the synergist piperonyl butoxide (42%) had the highest detection frequencies. Five other pyrethroids were detected in none or only one sample: fenpropathrin, pyrethrin I, pyrethrin II, prallethrin, and resmethrin. Overall the median detection frequency was 5%. At a 5% detection frequency, the pesticide wipes would require sample sizes range from 160 (disease prevalence 10%, relative risk 5) to 580,000 (disease prevalence 0.2%, relative risk 1.4) (Table 6).

Six of the nine HAAs and all four THMs were detected in ≥ 60% of water samples (Table 5). Detection of the HAAs ranged from 5% to 88% (median: 75%); and detection of the THMs ranged from 66% to 94% (median: 75%). Samples with this detection frequency required estimated sample sizes from 35 to 93,000 depending on the relative risk and the disease prevalence of interest (Table 6). The water VOCs were not well detected with the median detection frequency of 0%.

Table 2
Environmental sample collection times, by visit and sample type.

Visit type	Environmental samples	No.[a]	Median (IQR) sample collection time (min)[b]
Pre-pregnancy	Air samples: $PM_{2.5}$, VOCs[c], Carbonyls[c]	254	39 (35–58)
	Wipe sample: pesticides	272	8 (6–10)
Pregnancy	Vacuum: allergens/ endotoxin	713	20 (15–24)
	Water: THMs[c] and HAAs[c]	65	17 (15–20)
	Water: VOCs[c]	72	10 (9–14)
	Wipe: metals, pesticides, SVOCs	711	23 (19–28)
Child 6-month	Air: $PM_{2.5}$, VOCs[c], carbonyls[c], NO_2[c], O_3[c]	85	46 (35–58)
	Vacuum: allergens/ endotoxin	98	20 (15–21)
	Wipe: metals, pesticides, SVOCs	97	25 (21–33)

Abbreviations: HAAs, haloacetic acids; IQR, interquartile range: 25th–75th percentiles; $PM_{2.5}$, particulate matter 2.5 μm diameter; NO_2, nitrogen dioxide; O_3, ozone; SVOCs, semi-volatile organic compounds; THMs, trihalomethanes; VOCs, volatile organic compounds.

[a] Refers to the number of environmental sample collection forms or the number of interviews.

[b] Sample collection time based on the difference between start and stop times as recorded on sample collection forms.

[c] Sample only collected if subsample or trigger criteria were met.

4. Discussion

In this paper, we describe the feasibility and informative value of the environmental sample collection procedures from the NCS initial Vanguard Study, a study which collected a wide variety of environmental samples, which were analyzed for many different

Table 3
Air sample analyte detection frequencies, distributions of detected concentrations.

Analyte	N[a]	Mean limit of detection (LOD) (μg/m^3)	Detection frequency (%)	Median (IQR) of detected analyte concentrations (μg/m^3)
Particulate matter 2.5 μm ($PM_{2.5}$)	296	0.27	100	28 (16–51)
Nitrogen dioxide (NO_2)	54	0.09	100	3.3 (1.8–7.4)
Ozone (O_3)	14	1.48	36	10 (6.2–19)
Carbonyls				
Acetaldehyde	114	0.42	11	4.7 (2.5–9.7)
Acetone	114	0.38	23	26 (18–59)
Benzaldehyde	114	0.82	80	12 (8.4–16)
Crotonaldehyde	114	0.67	1	–
Formaldehyde	114	0.2	77	33 (22–47)
Glyoxal	114	0.24	22	23 (18–25)
Hexanaldehyde	114	0.9	89	7.4 (4.4–14)
Methylglyoxal	114	0.1	5	38 (20–46)
Propionaldehyde	114	0.53	1	–
Volatile organic compounds (VOCs)				
Benzene	35	1.31	57	4.9 (3.7–7.3)
Chloroform	36	1.51	17	14 (2.3–17)
1,4-Dichlorobenzene	39	1.57	15	33 (5.9–83)
Ethylbenzene	38	0.76	45	2.3 (1.6–3.3)
D-Limonene	40	1.86	80	17 (8.3–35)
Methyl tertiary-butyl ether	8[b]	1.61	0	–
alpha-Pinene	34	2.48	53	8.8 (5.7–17)
beta-Pinene	34	1.4	35	2.3 (1.8–4.5)
Styrene	30	2.03	3	3 (3–3)
Tetrachloroethene	34	2.03	0	–
Toluene	41	0.79	93	9.2 (3.8–23)
Trichloroethene	31	1.4	0	–
m,p-Xylenes	40	1.42	65	4.5 (3.1–8.9)
o-Xylene	35	1.13	40	3 (1.5–4.2)

Abbreviations: IQR, interquartile range: 25th-75th percentiles.

[a] Number differences refer to values excluded due to laboratory interferences or missing information, or delayed addition of analyte.
[b] MTBE concentration not available for most samples; analyte was added to the panel later.

chemicals, and obtained from a wide geographic area. We observed that the feasibility of the samples collected was high, while the informative value varied by sample type.

Although quite high, the air samples had the lowest overall sample collection rate (80%). These sample collection rates are consistent with NHANES and other children's exposure studies (Sexton, 2004; Jia et al., 2008) and likely do not bias the study data if the missingness is random. However, if missingness is correlated with an etiologically relevant factor, such as if air samples were less likely to be collected in low-income homes due to limited space, the missingness could present a challenge to study validity. We were not able to evaluate this explicitly, but found no evidence that sample collection rates differed between urban and rural areas. Additionally, we had a high degree of missingness by design as many air samples were triggered or subsampled, if these samples also had a high rate of non-collection, the study may not be sufficiently powered to evaluate the study hypotheses. The $PM_{2.5}$ sample was the most time-consuming collection, due to the required assembly and take-down of the air sampling stand and the calibration of the pump. The passive air samples were much less time consuming (estimated 7 min per sample). The sample detection frequencies of most air samples yielded required sample sizes that may be attainable study of children's environmental health depending on the prevalence of the disease of interest and the expected relative risk. The $PM_{2.5}$ and NO_2 samples were the most informative as they had detection frequencies of 100%, similar to other studies reviewed (Weisel et al., 2005). However, the high detection frequency of NO_2 was likely in part due to the requirement to sample primarily in the presence of a source. In addition, the detection frequency for $PM_{2.5}$ was based on a gravimetric analysis; chemical analysis of specific compounds may be lower.

Future studies of children's environmental health may be able to increase the feasibility of the air samples by incorporating passive aerosol samplers, which are increasing in precision (Arashiro and Leith, 2013). The informative value of the $PM_{2.5}$ samples could be enhanced if filters undergo additional analysis, such as chemical characterization, or reflectance to measure black carbon (Yan et al., 2011). Direct-reading instruments with data logging capabilities may have decreased sample collection time, and increased the informative value by allowing for assessment of peak exposures (Wells et al., 2013; National Research Council, 2012). However, study designers should consider the availability and cost of the device, the complex data management, and the instrument cleaning, maintenance, and calibration requirements before choosing a direct reading instrument.

The vacuum samples were moderately time consuming (median collection time of 20 min at each sample type). The vacuum samples were roughly twice as time consuming to collect than the wipe or water samples, and are only planned to measure allergens and endotoxin. The vacuum sample could be made more time-efficient per exposure measure by changing the collection procedure from the use of the DUSTREAM™ sampler to collection of bulk dust from the participants' vacuum cleaners for analysis to include chemicals such as pesticides, persistent pollutants, and metals. The NCS began piloting the collection of dust from the participant vacuum cleaners in 2011; initial estimates for these sample collections are 7 min, roughly 50% shorter than the DUSTREAM™ (NCS, 2011). The decrease in labor intensity is moderated by issues which could impact the measured chemical concentrations, such as the different vacuums, vacuuming frequencies, and bag changing practices of participants. In addition, some participants may not own a personal vacuum. Collection of dust from participants' vacuum cleaners has shown good

Table 4
Wipe sample analyte detection frequencies, distributions of detected concentrations.

Analyte	N[a]	Mean limit of detection (LOD) (μg/m^3)	Detection frequency (%)	Median (IQR) of detected analyte concentrations (μg/m^3)
Organochlorine				
alpha-Chlordane	803	0.004	15	0.011 (0.007–0.024)
gamma-Chlordane	798	0.0043	17	0.013 (0.0077–0.028)
4,4′-DDD	785	0.0016	3.6	0.0089 (0.0072–0.015)
4,4′-DDE	799	0.0017	5.5	0.0092 (0.005–0.021)
4,4′-DDT	801	0.0017	7.9	0.029 (0.011–0.08)
Heptachlor	803	0.0079	3	0.016 (0.012–0.033)
Organophosphate				
Chlorpyrifos	801	0.0075	12	0.027 (0.014–0.063)
Diazinon	801	0.0033	4.6	0.018 (0.0074–0.034)
Malathion	797	0.0047	0.75	0.91 (0.71–1.9)
Phenylpyrazole				
Fipronil	794	0.0071	22	0.052 (0.016–0.35)
Pyrethroid				
Allethrin	797	0.071	0.5	1.9 (0.39–3.3)
Bifenthrin	810	0.0018	32	0.023 (0.01–0.14)
Cyfluthrin	802	0.011	9.8	0.31 (0.12–0.98)
lambda-Cyhalothrin	798	0.0078	11	0.17 (0.053–0.65)
Cypermethrin	808	0.023	24	0.43 (0.14–2.5)
Deltamethrin	798	0.17	1.5	0.67 (0.57–5.5)
Esfenvalerate	797	0.1	2.3	0.51 (0.22–1.6)
Fenpropathrin	797	0.0071	0	–
Imiprothrin	798	0.085	2.5	1.1 (0.47–3.3)
cis-Permethrin	816	0.0047	48	0.082 (0.033–0.29)
trans-Permethrin	817	0.0061	48	0.12 (0.051–0.37)
Prallethrin	797	0.074	0.25	9.9 (1.6–18)
Pyrethrin I	797	0.27	0	–
Pyrethrin II	797	0.26	0	–
Resmethrin	797	0.0045	0	–
Sumithrin	798	0.0056	2.6	0.18 (0.095–2.3)
Tetramethrin	799	0.0028	5.4	0.2 (0.081–0.72)
Insecticide synergist				
Piperonyl butoxide	808	0.0022	42	0.071 (0.023–0.29)

Abbreviations: 4,4′-DDD, dichlorodiphenyldichloroethane; 4,4′-DDE, dichlorodiphenyldichloroethylene; 4,4′-DDT, dichlorodiphenyltrichloroethane; IQR, interquartile range: 25th-75th percentiles.

[a] Number differences refer to values excluded due to laboratory interferences or missing information.

correlation with more standardized time- and labor-intensive procedures for a range of chemical contaminants (Colt et al., 2008, 1998).

The wipe samples were quite feasible, given they were very time-efficient collections with a high collection rate. The pesticide wipe sample, the only wipe analyzed to date, had a low informative value due to the low analyte detection frequencies and thus large (>1700) sample sizes required to detect health effects such as musculoskeletal birth defects and autism. The low analyte detection frequency with wipe samples also has been observed in the American Healthy Homes Survey (AHHS) (Stout et al., 2009). The informative value of the wipe samples could be improved by changing the wipe wetting agent from water to isopropanol (Deziel et al., 2011). Alternatively, pesticide wipe samples could be replaced with bulk dust collection, which has been shown to yield higher detection frequencies (Colt et al., 2005).

Water samples were feasible as they had short collection times and had high collection rates. The water THM and HAA samples had high detection frequencies and therefore high informative value. Other studies have reported similar detection frequency for water THM and HAA samples (Weisel et al., 2005,1999; Loo et al., 2010; Diette et al., 2007; Lynberg et al., 2001). The water VOCs samples were not informative in this study, as the median analyte detection frequency was 0%. One other study reviewed had a higher frequency of detection of VOCs in domestic wells, (Rowe et al., 2007) but given the small number of samples collected in our study ($n=75$) and a lack readily available address information we could not evaluate whether factors such as proximity to sources may have caused these differences.

One strategy designers of future children's environmental health studies could consider to increase analyte detection frequency is pooling samples from individuals by subpopulations such as, age, race, gender, and geographic region. Sample pooling allows for estimation of the mean exposure within the different pooled sub-groups and reduces analytic costs by decreasing the number of samples analyzed (Caudill, 2008). However, if the study is longitudinal in nature, designers must be careful in selecting pools to ensure they do not lose important measures at etiologically relevant time points.

The reasons for failure to collect environmental samples could not be determined because in those instances, hard-copy forms were rarely completed. There was no study system in place that managed submission of the hard-copy forms, likely contributing to this issue. We cannot determine which samples were not obtained primarily due to participant refusal and which were not obtained due to equipment problems. Future children's environmental health pilot studies should use electronic sample collection forms that require entry of reasons for the failure to collect a sample to allow for evaluation of reasons for missingness, a potential source of bias.

The use of the calculation of required sample sizes to detect a given relative risk was a useful tool for characterizing the informative value, but it has some limitations and assumptions. We used prevalences of important diseases in children's environmental health and risks of a magnitude observed in epidemiologic studies, but we did not evaluate the plausibility of each exposure–disease scenario. We also did not include an attrition factor in our calculations. Additionally, we substituted the exposure prevalence

Table 5
Water sample analyte detection frequencies, distributions of detected concentrations.

Analyte	N[a]	Mean limit of detection (LOD) (μg/m^3)	Detection frequency (%)	Median (IQR) of detected analyte concentrations (μg/m^3)
Community water HAAs				
Bromochloroacetic acid	67	0.31	88	1.5 (0.66–2.7)
Bromodichloroacetic acid	67	0.3	84	1.8 (1.2–2.7)
Chlorodibromoacetic acid	67	0.42	60	1.2 (1.2–1.2)
Dibromoacetic acid	67	0.31	75	1.2 (0.66–2.1)
Dichloroacetic acid	66	0.36	80	5.2 (2.8–9.5)
Monobromoacetic acid	67	0.12	5	0.56 (0.56–0.56)
Monochloroacetic acid	67	0.77	16	1.4 (1.4–2.2)
Tribromoacetic acid	66	0.69	15	2.3 (2.3–2.3)
Trichloroacetic acid	66	0.36	76	3.4 (1.8–9.2)
Community water THMs				
Bromodichloromethane	68	0.11	94	4.8 (2.1–9.5)
Bromoform	68	0.12	66	1.1 (0.31–2.8)
Chloroform	68	0.17	91	12 (3.6–28)
Dibromochloromethane	68	0.1	91	2.6 (1.3–5.7)
Well water VOCs				
Acetone	69	2.7	4	7.3 (7.3–12)
Bromodichloromethane	68	0.1	6	2.1 (0.9–2.7)
Bromoform	68	0.12	2	0.7 (0.7–0.7)
Carbon tetrachloride	68	0.11	2	0.3 (0.3–0.3)
Chloroform	68	0.14	7	5.9 (2.1–9)
Dibromochloromethane	68	0.1	6	0.85 (0.3–2)
1,4-Dichlorobenzene	68	0.1	2	0.28 (0.28–0.28)
Dichlorodifluoromethane	68	0.09	3	0.29 (0.29–0.29)
Ethylbenzene	68	0.15	2	0.31 (0.31–0.31)
Styrene	68	0.15	4	0.33 (0.33–0.33)
Tetrahydrofuran	68	0.71	9	2.8 (2.8–2.9)
Trichloroethene	68	0.1	2	0.3 (0.3–0.3)
1,2,4-Trimethylbenzene	68	0.13	2	0.31 (0.31–0.31)

Abbreviations: HAAs, haloacetic acids; IQR, interquartile range: 25th-75th percentiles. THMs, trihalomethanes; VOCs, volatile organic compounds.

[a] Number differences refer to values excluded due to laboratory interferences or missing information.

with a dichotomization of analyte detection in an environmental sample. This is overly simplistic for a few reasons. In most epidemiological models, one would not dichotomize exposure based on the detection frequency; one would use the continuous analyte concentration, or another more refined categorization. Our approach also assumes any concentration above the detection limit is health-relevant, which for many of these compounds that level is unknown. Finally, the analyte concentrations in the environmental sample alone may not be sufficient to characterize exposure. For example, when studying exposures through tap water, an epidemiologic study may consider other factors such as additional filtration practices after the collection point and the consumption of bottled water.

A limitation of our analysis is that we did not present the cost of sample collection. We did present the time to collect environmental samples at the visits, which is a factor in the per sample labor costs. Laboratory and environmental supply cost estimates for the samples in this phase are available, but given that these costs vary from year to year and often depend on contract negotiations, we thought evaluations of these data might lead to biased or subjective results. Other epidemiologic studies of children's health should strongly consider methods for optimizing costs of their exposure assessment parameters, such as using the asymptotic relative efficiency (Armstrong, 1996).

5. Conclusions

Feasibility and informative value of environmental sample collection are critically important considerations in the planning

Table 6
Sample size estimates based on sample median detection frequencies.

Disease prevalence (%)	Relative risk	Exposure prevalence			
		> 50% air NO_2; air $PM_{2.5}$; water HAAs; water THMs	35% air O_3; air VOCs	20% air carbonyls	5% wipe pesticides
0.2	1.4	93,000	104,000	150,000	508,000
(example: musculoskeletal birth defects)	2.5	9600	11,000	16,000	55,000
	5	2300	2700	4000	14,000
1.5	1.4	12,200	13,600	20,000	67,000
(example: autism)	2.5	1300	1500	2100	7200
	5	300	350	500	1700
10.0	1.4	1700	1900	2600	8900
(example: asthma)	2.5	160	180	260	900
	5	35	40	50	160

Abbreviations: HAAs, haloacetic acids; $PM_{2.5}$, particulate matter 2.5 μm diameter; NO_2, nitrogen dioxide; O_3, ozone; SVOCs, semi-volatile organic compounds; THMs, trihalomethanes; VOCs, volatile organic compounds.

and design of children's environmental health studies. We have provided data for these factors across a broad range of sample types and chemical analytes. This information could be used in conjunction with the goals and hypotheses of future studies to inform the optimal study design for future environmental health cohort studies.

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